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## Introduction

### The Use of Animal Research in Developing Treatments for Human Motor Disorders: Brain-Computer Interfaces and the Regeneration of Damaged Brain Circuits

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This issue of the *ILAR Journal* is devoted to animal models of human movement disorders. It is not possible to cover this vast topic in a few short articles, but we hope that the contributing researchers' descriptions of research models and results will inform, guide, and promote further research on motor disorders.

The research field is broad because so much of the nervous system relates to motor function. It is sometimes said that animals have brains because they move faster than plants. Being able to move about clearly puts a premium on having a large brain that can analyze and use both previous experience and ongoing sensory information in order to guide and control motor systems and thus produce skillful and productive behaviors. For humans in particular, our large, complex brains allow a range of skilled performances that greatly exceeds that of any other mammal. We can especially marvel at the performance of our most accomplished musicians and athletes. The ability to develop these skills, which frequently require years of devoted, specialized practice, indicates that general-purpose brain circuits can be rewired through use in order to perfect a variety of specific motor feats. This same flexibility in the use of brain circuits enables us to compensate to various extents for brain injuries, and thereby maintain capabilities as brain impairments progress or recover capabilities lost after injuries.

Animal research that is relevant to the treatment of human motor disorders is of several types:

- Studies that provide a better understanding of how sensorimotor systems work and how they are organized can guide clinical research and treatments.
- The results of studies focused on understanding the ability of brain systems to reorganize with training can help formulations of therapeutic treatments and suggest interventions that might promote useful brain plasticity.
- Animal studies of the abilities of brain circuits to self-

repair after damage have obvious relevance. Furthermore, as some of this repair involves the growth or regrowth of brain pathways and local circuits, animal studies can be useful in attempts to explain and evaluate treatments that promote such growth.

- Animal studies can help the development and evaluation of recent treatments for human motor disorders that include the placement of electrodes in the brain to stimulate parts of motor systems or to read signals that can be used to instruct computers and mechanical aides.
- Animal studies can provide an understanding of the genetic, molecular, and cellular components of human motor disorders, and can help in evaluations of drug and other treatment protocols for effectiveness. This category of animal research includes studies that induce in animals the components of human motor disorders so that treatments for these disorders can be evaluated. Clearly, this last, large category can be expanded and subdivided to include the many types of animal research that address human motor disorders.

The articles in this issue represent a diverse selection of research efforts in all of these categories. For additional information on animal models of movement disorders, the reader is referred to a recent overview volume by LeDoux (2005).

This Introduction complements the accompanying articles with brief overviews of two types of motor disorder-related animal research. The first type of research aims to help disabled humans by using information from their brains to instruct machines to do things that they can no longer do for themselves. The second investigates ways to promote nervous system regeneration in order to enhance recovery from spinal cord and brain injuries.

### The Potential Use of Brain-Computer Interfaces to Partially Compensate for Motor Impairments

Human motor disorders vary greatly in severity. Amyotrophic lateral sclerosis (ALS), for example, can lead to extensive and almost total impairments in motor function. The well-known astrophysicist Stephen Hawking is severely im-

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paired by ALS, but is able to use the limited remaining motor function of his face to activate an infrared motion detector that signals instructions to a computer and enables him to communicate in both written text and synthesized speech. In more serious cases, when even eye or finger movements cannot be used to direct the computer, it is possible to train (with great difficulty) patients to signal by altering their brain wave patterns to give yes or no answers while scalp electrodes record their brain activity (Hinterberger et al. 2003; Karim et al. 2006; Kübler and Neumann 2005; Parker 2003). But recorded brain waves have been of very limited use so far in helping patients compensate for extensive impairments in motor control.

A more promising—but more risky—approach is to record directly from arrays of neurons in the brain (Nicoletti 2001; Schwartz 2004). If there are neurons in primary motor cortex, which is the final cortical output of motor intentions, there is also potential for acquiring information that normally serves to produce voluntary motor behavior. Even though this information can no longer be used in the control of muscles and movements, it can still be used by a brain-computer-machine interface to produce prompt and meaningful communication, control transportation devices, and manipulate robotic arms that perform the tasks of real arms. The feasibility of this approach has already been demonstrated in a tetraplegic human volunteer whose paralysis resulted from a spinal cord injury (Hochberg et al. 2006). An array of electrodes was implanted in motor cortex of this volunteer, and his imagined limb movements were used to modulate the firing rates of recorded neurons. The recorded responses of these neurons in motor cortex were used, in turn, to guide a computer cursor or control a robotic arm. This important step in restoring function to patients came after many years of pioneering animal research that evaluated types of electrodes and demonstrated the usefulness of signals from assemblies of recorded neurons (Carmena et al. 2003; Chapin et al. 1999; Nicoletti et al. 1998, 2003; Sathianam et al. 2006; Taylor et al. 2002).

Further animal research and more development and testing are needed, as current recording arrays are not reliable in terms of consistency, durability, and tissue compatibility. More research can also help decode neuron signals, and determine the numbers and placement of electrodes to record useful outputs. While the challenge of recording directly from neurons in the human brain as a therapeutic measure requires additional exploration and testing, electrodes for stimulating neurons are now commonly placed in human brains for treatments of motor disorders, especially Parkinson's disease (Lozano et al. 2002; Perlmutter and Mink 2006). With further research, safe and useful procedures for recording from neurons in the human brain may emerge in the near future.

## Regenerating Damaged Neural Pathways

Spinal cord injury is a major cause of motor and sensory disorders in humans. An estimated 2.5 million people live

with spinal cord injury (Thuret et al. 2006). Medical treatments have traditionally focused on managing patients to prevent complications and on training them to adapt to a life with major motor impairments. But spinal cord injuries seldom result in complete transections, and the preserved pathways determine what functions remain or will gradually recover. That some recovery usually takes place indicates that the remaining connections somehow become more useful, because severed pathways do not normally regenerate.

Animal studies have helped us understand why partial recovery is possible and how such recoveries can be promoted (Kaas 2001). Much of the research has been done on rats (e.g., Massey et al. 2006; Onifer et al., this issue), but research on monkeys may be even more effective in promoting progress (Courtine et al. 2007). Courtine and colleagues (2007) have described the advantages and disadvantages of research on contusion and on partial and complete spinal cord lesions in nonhuman primates. However, just as spinal cord injury seriously impairs the quality of life for humans, animal studies in this area present special challenges to investigators, who should make every effort to minimize adverse consequences for the experimental animals (see Wallace and Sikoski in this issue).

One approach not considered would be to study monkeys or other mammals with spinal cord injuries that have occurred by accident, as they do in humans. Such an approach has been used to study the brain changes that take place in monkeys after therapeutic amputation of an accidentally damaged limb. Much can be learned from only a few cases (e.g., Florence and Kaas 1995). But unintended spinal cord injuries are rare in laboratory animals.

An alternative is to study the effects of lesions that produce a limited sensory or motor loss in animals, identify the mechanisms of spontaneous recovery, and develop treatments to promote and enhance these recoveries. Investigators and clinicians could then draw inferences from the results of these studies to inform and guide therapeutic treatments in humans. One version of this approach has been to partially cut afferents of the hands of monkeys in the dorsal roots of peripheral nerves and then monitor brain changes and improvements in hand use (see Darian-Smith in this issue). The intention was to impair the skilled use of the hand through the loss of sensory control. The results indicate that even a few surviving afferents—so sparse that they initially fail to activate somatosensory cortex—gain strength over weeks of recovery, so that large numbers of neurons in cortex are activated, and considerable skilled use of the hand returns. Similar procedures have severed most of the ascending afferents in the dorsal columns of the spinal cord at a high cervical level, leaving only a few intact branches of afferents from the hand in the dorsal column pathway while preserving afferent terminations on neurons in the spinal cord and second-order pathways such as the spinothalamic pathways. The lesioned monkeys appear normal to the casual observer as they locomote and climb about, but during the first few weeks after the procedure skilled movements of the hand are lost due to a lack of

sensory guidance (Jain et al. 1997). Gradually, however, the few preserved afferents from the hand sprout in the lower brain stem relay nucleus (Jain et al. 2000) to activate more neurons than these afferents normally do, and this effect amplifies in the contralateral thalamus and somatosensory cortex over a few weeks of recovery so that the remaining afferents play a greater than normal role in guiding hand use. Thus, considerable recovery of skilled hand use can occur if even a few of the relevant afferents from the hand are preserved.

Further research could usefully evaluate the potential of therapies designed to enhance recoveries beyond those that occur spontaneously. One approach would be to consider treatments that promote further productive sprouting as well as use of remaining spinal cord afferents, or even the re-growth of some axons past the lesion site. Two types of treatment seem to have promise. First, there is considerable evidence that neurite growth is normally inhibited by components present in oligodendrocytes and central nervous system myelin (Schwab 2004; Yiu and He 2006). An antibody to one of these inhibitory factors, Nogo-A, has been used to counter the inhibition and enhance regenerative sprouting and axon elongation. As one example, the application of anti-Nogo-A antibody to the region of lesions of the corticospinal tract of monkeys resulted in the sprouting of descending neurites that grew through and around the lesion sites, resulting in improved manual dexterity (Fouad et al. 2004; Freund et al. 2007). Given the great impact that even a few functioning axons can have, this treatment has great potential.

Another treatment that seems promising is to digest the perineuronal network around neuron groups that impedes the sprouting of neurites (Silver and Miller 2004). In rats with partial section of the dorsal columns, digestion of the perineuronal network in the cuneate relay nucleus of the dorsal column complex enhanced sprouting in the nucleus and the reactivation of neurons (Massey et al. 2006). Other types of therapeutic interventions, such as the transplantation of cells or tissue to the lesion site to create an environment for regeneration, are also under study (Thuret et al. 2006).

Some of the treatments or combinations of treatments studied in these animal models are likely to be of great benefit to those suffering from spinal cord and other central nervous system injuries. Of course, current efforts to discover treatments that promote brain plasticity and recoveries from injuries build on a long history of animal studies that have demonstrated the great potential of the mature nervous system for plasticity and functional reorganization (see, for example, the review of studies in Kaas 2001).

## Summary

As a complement to the articles in this issue, this Introduction has focused on two areas of animal research that may provide knowledge that can promote the development of

interventions and treatments of patients with major impairments of motor control. One type of research seeks ways to promote the regeneration of damaged and other nervous system pathways that are used in sensorimotor control of behavior. The other type of research focuses on developing ways to record from motor neurons in human brains so that intentions can be read when motor functions fail. Both types of research have primarily used rats as experimental animals, but a growing number of researchers are now using monkeys. These and other types of animal research on movements disorders challenge investigators to develop procedures that minimize the number of animals needed to produce informative results and that minimize the stress and discomfort of these experimental animals.

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